Review

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Serotonin Transporter Polymorphism in Relation to Depression

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Abstract – Serotonin is regarded as one of the most important factors in modern psychiatry and a significant amount of research is associated with that neurotransmitter in some way. Serotonin transporter and its various polymorphisms are implied to be connected with various psychiatric disorders, mostly depression and suicide. In light of that fact, this review article will try to address new and current data regarding serotonin transporter polymorphisms and their association with depression. As this area of research in psychiatry is constantly growing and nowadays incorporates various other factors than was the case previously it was necessary to provide a brief overview of those factors. Therefore, data regarding serotonin transporter polymorphisms and its relation with gene-environment interactions, biological stress reactivity and personality traits and their possible combined effects on depression are discussed. No matter how big is the quantum of knowledge and research regarding serotonin, the only constant finding when analyzing the possible association of serotonin transporter polymorphism and depression are inconsistent conclusions. Therefore it can be concluded that molecular and neural mechanisms that underlie the interplay of genes, environmental adversity and personality traits that constitute disease risk remain incompletely understood. Due to these inconsistent conclusions, further genotyping of SLC6A4 and other genes is necessary, as well as studies performed on bigger samples of participants. Factors like life stress and environmental factors, which may contribute to increased vulnerability in susceptible individuals, should also be more extensively addressed as they may prove be the key to timely treatment and effective preventive strategies.

Key words: serotonin transporter, serotonin transporter polymorphism, depression

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Introduction

Much has been written about serotonin, its physiology and effects through the course of time but we still cannot claim to know everything about this neurotransmitter. Serotonin is regarded as one of the most important factors in modern psychiatry and therefore is no wonder that many studies deal with serotonin in one way or another. Research regarding serotonin transporter is no exception and this article will try to pro-

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vide a closer and more concise report of research conducted thus far.

5-hydroxytryptamine, or just serotonin, plays an important role in neurodevelopment and functioning of the brain. It is involved in regulation of a wide variety of functions and behaviors such as appetite, sleep, mood, motor activity, emotions and altered neuroendocrine function [1]. Serotonin functions as a short-range neurotransmitter, a paracrine neuronal modulator at a number of different receptors and as a long-range signaling modulator. Its effects are multiple and spread throughout the organism via plasma, platelet, neuroendocrine, gut, adrenal and other peripheral systems across many species [2].

The serotonin transporter (5-HTT) is a monoamine transporter protein with a crucial role in serotoninergic function. It terminates synaptic actions of 5-HT and transports it from synaptic spaces into presynaptic neurons, effectively recycling it into the neurotransmitter pool [3]. 5-HTT also has a major role in regulation of the homeostasis of spatial distribution and intensity of 5-HT signals with 5-HT receptors [4-6]. Serotonin transporter is encoded by the gene termed SLC6A4 that maps to chromosome 17q11.2. It is composed of 15 exons spanning about 40 kb. The sequence of the transcript predicts a protein comprised of 630 amino acids with 12 transmembrane domains. Alternative promoters, differential splicing involving exons 1A, B, and C, and 30-untranslated-region variability result in multiple mRNA species, as well as specific polymorphisms, that are likely to regulate gene expression SLC6A4 in humans. Best studied is the promoter region polymorphism, 5-HTTLPR, which together with two intrinsic single nucleotide polymorphisms (SNP's) [rs25531 and rs25532], all located upstream of the transcription start site, modulate the transcriptional activity of SLC6A4 [2,7-9]. Additional variants at the SLC6A4 locus include a functional variable number of tandem repeats (VNTR) polymorphism in intron 2 and a number of other coding region SNP's that change the structure or function of the transporter protein, such as I425V and G56A [2,8,10-13]. Most of these SNP's are rare [7,14].

As mentioned, best studied polymorphisms of the serotonin system are linked with the 5-HTT gene-linked polymorphic region (5-HTTLPR), a repetitive element of varying length located in the promoter region of SLC6A4. It modulates the transcriptional activity of human 5-HTT. Alleles of the serotonin transporter polymorphism are most commonly composed of either fourteen (short or S allele) or sixteen (long or L allele) repeated elements which affect transporter expression and function [15]. However, other alleles have also been identified at low frequency, including 15-, 18-, 19-, 20-, and 22-repeat alleles, with various additional SNPs distinguishing some repeats [16]. More recently, 5-HTTLPR polymorphisms have been researched from a newer viewpoint. Specifically, an A/G nucleotide substitution in the L allele renders the 5-HTTLPR tri-allelic with the functional variants of the L allele designated as LA and LG [17]. Similar was observed for the S allele and it was subdivided into SA and SG18. It was observed that the A variant - LA produces high levels of mRNA and that the G variant - LG is equivalent to the S allele [7,19,20].

Other polymorphisms in this gene that have been reported include: functional VNTR polymorphism comprised of 9, 10, or 12 copies of a 16/17 bp element located in

intron 2 of the serotonin transporter gene, termed Stin2 VNTR and a single nucleotide polymorphism (SNP) in the 30 untranslated region (UTR) [4,21-23].

Short and long alleles of the 5-HTTLPR have different transcription rates, which leads to different SERT mRNA, protein levels and 5-HT uptake activity [4]. The long allele has been associated with a two- to threefold more efficient transcription of the gene, compared to the short allele, which would be less active resulting in reduced serotonin uptake [18,23,24]. Consistently, Greenberg and associates have established that in human healthy males, the L allele is associated with more rapid initial platelet 5-HT uptake [25]. However, a study by Kaiser and associates did not replicate this observation [26]. Hanna and associates found that subjects with LL and LS genotypes exhibit significantly higher platelet 5-HT levels than those with the SS genotype [27]. Several newer studies found that the S allele of 5-HTTLPR, as well as rs25531 and rs25532 SNP variants (and most likely the shorter STin2 VNTR 9 and 10 repeat alleles) might cause 50–80% lower expression levels of SERT. In contrast, higher-expressing SERT alleles can lead to a 5-fold greater serotonin uptake capacity. Murphy and associates concluded that combinations of the frequent SLC6A4 variants, and possibly also the less common variants, may act together to confer from five to twenty-fold differences in SERT expression and function levels [2]. All that being said transcriptional efficiency was measured mostly in vitro, but in vivo long-term influence of the two alleles of 5-HTTLPR polymorphism on serotonin pathways remains mostly unknown [28].

Several researches established one more important aspect for further study of serotonin transporter polymorphism. That aspect is racial variations, as frequencies of the L and S alleles vary among races [5,7,22]. Williams and associates reported an L-allele frequency of more than 70% in African and African–Americans, a frequency of roughly 50% in Europeans and a 30% or lower L-allele frequency in the Japanese population [1]. Because the 5-HTTLPR is a functional polymorphism these differences might result in different baseline levels of relevant measurements in the serotonergic system, and different strengths of the association between this polymorphism and mental illnesses in various ethnic groups [33].

In order to examine the effects of serotonin transporter reduction and deficiency, experimental models on mice have shown that the SERT-deficient state results in failure to re-accumulate released serotonin and in turn leads to decrease of serotonin brain-tissue concentrations by 40-60% [29-31]. In these mice blood plasma and platelets are devoid of serotonin and most peripheral organs have markedly depleted serotonin levels [29,31]. However, SERT reduced mice do not express similar traits. Therefore, the loss of one SLC6A4 allele leads to a decrease in many transporter functions, but this single copy of a SLC6A4 allele is adequate to maintain most overall tissue serotonin homeostasis [2].

As far as the VNTR region is concerned, it has been suggested that it may act as a transcriptional regulator of the serotonin transporter gene in allele-dependent manner, with 12 repeat allele having stronger enhancer-like properties than 10 repeat allele [32]. Also, it has been noted that individuals homozygous for the 12-repeat allele had lower affinity of 5-HT uptake than individuals who had the 10/9 genotype [16].

Serotonin Transporter Polymorphism and its Association with Psychiatric Disorders

There is a vast amount of evidence supporting the association between the serotonin transporter polymorphism and various psychiatric disorders and phenotypes. S allele was shown to be associated with a variety of emotional disorders and psychopathological traits such as the following: depression [34], suicidality [33,35], bipolar affective disorder [36,37], schizophrenia [38], anxiety disorders [22,39-41], post-traumatic stress disorder [42], panic disorder [43,44], panic disorder comorbid with bipolar disorder [45], obsessive-compulsive disorder [46], eating disorders, impulsivity–aggression, certain types of alcoholism, autism and Alzheimer's disease [28,47].

All that being said, reports on the association of the 5-HTTLPR with mental disorders have produced inconsistent findings. Several studies report lack of association of the S allele or the SS genotype to most of the aforementioned conditions [48-51]. According to the research of Veletza and associates, some reports even claim that the L allele and the LL genotype constitute risk factors for certain conditions including adolescent hyperkinetic disorder, adolescent violence, obsessive–compulsive disorder, bulimia, and schizoid personality disorder [28].

Regarding the VNTR polymorphism, there is strong evidence for increased frequency of allele 12 in subjects with bipolar disorder [43,52]. Additionally, allele 9 has been associated with unipolar disorder [53,54]. Finally, an increased frequency of the 10 allele together with the L allele of the promoter polymorphism was observed in a suicide cohort [32]. Therefore, most of the evidence suggests that this polymorphism is functional and may influence affective disorders. On the other hand, no associations of affective disorders with the intronic VNTR were found in studies performed on German, Japanese and Chinese populations [52]. As the association with depression has not always been reproducible there is a need to determine the exact association between the VNTR polymorphism and depressive phenotype [16].

Somatic illnesses were also investigated in regard to their association with the serotonin transporter polymorphism. Several studies showed a relationship between depression and the S allele, as a study by Gilbert and associates performed in a population of head-neck patients [55]. On the other hand, Phillips-Bute and associates found that the LL, and not the SS genotype was associated with increased depressive symptoms one year after coronary artery bypass graft surgery, and that the presence of the L allele was associated with increased incidence of adverse cardiac events [56]. Grassi and associates found no association between 5-HTTLPR genotypes, serious life events and depression in breast cancer patients [57]. Therefore research on somatic illnesses is also characterized by inconsistent findings.

Research among psychiatrically healthy individuals showed that individuals homozygous for the S allele exhibit higher levels of depressivity and are more likely to have first-degree relatives with a history of depression [28]. Focusing more on depression, research about the association between 5-HTTLPR polymorphism and depression has produced inconsistent findings [58]. Several researches linked the functional polymorphism within the promoter region of the 5-HTTLPR to major depressive disorder [59-62]. PET stud-

ies also suggest widespread impairment of 5-HT function, while postmortem studies report abnormal reductions of brain 5-HT transporter sites in depression [47]. Furthermore, Cervilla and associates found that the SS genotype may play a small but independent role in increasing the risk for major depression [63]. S allele of the 5-HTTLPR has also been associated with increased risk of developing major depression in patients with chronic psychotic disorders [64], as well as geriatric patients [65]. Moreover, S allele was found to be more frequent in depressed patients [43] and suicide victims [66], while others have not confirmed these findings [51,67]. Brown and associates reviewed a number of studies and found no evidence for more than a small association of 5-HTTLPR with rates of depression and concluded that the polymorphism has at best an effect of modest size [68]. Newer studies focusing on the tri-allelic 5-HTTLPR polymorphism have established that the SS genotype of the tri-allelic 5-HTTLPR polymorphism may be a risk factor that increases the susceptibility to major depression, at least in male Chinese population [69].

Several studies and reviews suggested the possibility that 5-HTTLPR may not be directly associated with depression or suicide, but may rather modulate the serotonergic response to life stress [70-73]. Indeed, most contemporary theories concerning the role of genes in the onset of depression are stress-diathesis theories. These theories are based on the fact that the S allele has been shown to interact with stressful life events (SLE) to predict depression with remarkable consistency [9-16]. Practically the only exceptions being studies by Surtees and Gillespie [74-75]. In addition, 5-HTTLPR may predispose to depression in patients with severe medical illnesses that are associated with ongoing chronic stress [76,77]. Therefore one might expect to find a direct effect of the 5-HTTLPR polymorphism on depression in groups of chronically ill patients who are under considerable amounts of stress. That was confirmed in several studies where the S allele has been associated with depression in patients with Parkinson's disease, stroke, hip fracture and acute coronary syndrome [77].

Serotonin Transporter Polymorphism and its Association with Suicide

Special interest of psychiatry was always directed towards the problem of suicide. Therefore, it is of no surprise that many studies examined the possible association between serotonin transporter, its polymorphisms and suicidal behavior. As a result, several studies and meta-analyses [35,78] found evidence for a significant association of the S allele and SS genotype with suicidal behavior. However, research results have not been unanimous [79]. Similar was observed for the STin2 shorter 10 allele [2,79]. Furthermore, S allele of the 5-HTTLPR polymorphism was associated particularly with violent suicide attempts [33,78,80]. It was also shown that the S allele confers increased short term risk of subsequent suicide attempts following a suicide attempt [47]. Joiner and associates reported that family history of severe suicidality was more common among participants with the SS genotype than among others [61].

Post-mortem study which showed a diffuse reduction of 5-HT transporter binding in the prefrontal cortex of individuals with depression who died of suicide substantiated the link between abnormalities in 5-HT transporter function, depression and suicidal behavior [50]. However, 5-HTTLPR poly-

morphisms did not explain lower prefrontal cortex 5-HT transporter binding [47].

Although all findings mentioned above might suggest that a genetic alteration of the serotonergic system could predispose people to psychiatric diseases and suicide, the exact effect and role of 5-HTTLPR in genetics of suicide is still unclear and should be investigated further in future studies [18]. That is especially the case because several studies have not confirmed the association between the S allele and suicidal behavior [18,47,81].

Serotonin Transporter Polymorphism and its Association with Antidepressants Use

Changes in serotonin transporter alter the expression and/or function of most, if not all, serotonin receptors as well as the synthesis, clearance and metabolism of serotonin. These changes have important clinical implications for serotonin targeted psychopharmacotherapy as they might interfere or negate the effects of medication. These psychopharmacs include serotonin reuptake inhibitors (SRI's), selective serotonin reuptake inhibitors (SSRI's) and combined serotonin-norepinephrine reuptake inhibitors (SNRI's).

When taking a closer look at the 5-HTTLPR polymorphism, it is unclear why the S allele carriers would be disadvantageous to metabolism of serotonin. That is especially the case since reduced serotonin transporter function induced by SSRI's and other serotonin targeted antidepressants improves depression and impulsiveness (two conditions frequently associated with suicidal behavior). However, majority of studies and meta-analyses that examined the association between the serotonin transporter polymorphism and therapeutic response to SSRI's found the SS genotype and S allele associated with lower antidepressant efficacy, compared with patients with the LL genotype [82-89] although this has been disputed [90,91]. All of the nowadays known SSRI antidepressants have been investigated in regard to their therapeutic efficacy associated with 5-HTTLPR polymorphisms. Arias and associates reported a significant association between the S allele and no clinical remission after 3 months of treatment with citalopram [85,92]. Smeraldi and associates have shown that subjects with LL and LS genotype responded significantly better to fluvoxamine than subjects with the SS genotype [93]. Patients with the LL genotype respond more favorably and faster to paroxetine [83,94]. Similarly, patients with the LL genotype respond faster to sertraline than those with the SS genotype [95]. Rausch and associates have reported an association between the LL genotype and improved response to fluoxetine [96]. These studies suggest a clinically significant effect of increased baseline transcriptional activity and serotonin reuptake to SSRI response, due in part to polymorphic variation within the gene. However, these findings may apply primarily to Caucasian populations, as several studies reported associations between the S allele and more favorable treatment outcomes in Asian populations [89,90,97].

Serotonin transporter polymorphism has not only been associated with therapeutic responses but also with various adverse events of serotonergic psychopharmacs. Several studies found greater numbers and a greater variety of side effects during SSRI treatment in S allele or SS genotype individuals [88,98-101]. More specifically, Perlis and associates reported a 3.5-fold greater incidence of insomnia and a 9.5-fold greater incidence of agitation during treatment with fluoxetine in

individuals with the SS genotype compared to SL or LL individuals [98]. Hu and associates found that the S allele and SS genotype were strongly associated with intolerance to citalopram treatment [102]. In bipolar patients treated with serotonergic antidepressants, a 5.3-fold higher incidence of hypomania as a side effect occurred with the SS genotype compared to the other genotypes [103] and S allele carriers had higher rates of switching from depression to mania [3].

One explanation about why humans with the SS genotype and mice with reduced serotonin transporter have deficient responses to antidepressants is that a "plateau" effect may be responsible. That basically means that further inhibition of serotonin transporter activity might not be meaningful or adequate [2].

Everything stated leads us to conclude that it is very important to determine individual's genotype as it can influence therapeutic efficacy and adverse event profile of SSRI's and other serotonin targeted antidepressants.

Additional Factors Associated with Interaction of Depression and Serotonin System

Gene-environment Interactions - Serious Life Events

Connection between depression and the serotonin system has been examined and substantiated very often, but only recently research focused on the link between serotonin and stress, as well as their combined influence on depression. Scientific research has identified several factors with at least some effect on the mentioned association of serotonin transporter polymorphism and depression, and those are: gene-environment interactions (GxE), biological stress reactivity and personality traits, namely neuroticism.

Considering the multifactorial etiology of affective disorders idea has emerged that environmental factors should be involved in the genetic assessments, the so called gene-environment interactions or GxE. As already mentioned, majority of studies in this area have investigated exposure to stressful life events (SLE) as environmental factors. Evidence for gene–environment interaction (GxE) involving the polymorphism in the promoter of the serotonin transporter genotype (5-HTTLPR) and adult depression was first reported by Caspi and associates [34]. In this study S allele carriers showed more severe depressive symptoms and were at greater risk to develop depression compared with the LL genotype. In addition, Zalsman and associates found that the S allele predicted more lifetime depressive episodes [77]. Recent meta-analysis however did not provide evidence of clear association [104]. Research results on first onset of depression found that S allele carriers were associated with the presence of SLE prior to onset of depression [59]. Furthermore, number of studies confirmed the interaction between 5-HTTLPR and SLE in predicting onset of depression [105-107], severity of depressive symptoms [77] and suicidal ideation [108]. These findings were confirmed by Kendler and associates who reported that individuals homozygous for the S allele are more sensitive to the depressogenic effect of serious life events than L allele carriers [105]. Several studies confirmed these findings [106,109-111] including research on the role of serotonin in animals [51], others not completely [70,112], whereas some have failed to establish any gene-environment interaction [74,75,113-116] or even an effect in the opposite direction [117-119] compared

to the original findings by Caspi and associates [34]. Kendler and associates also noticed that the association between SLE and depression declines with increasing number of depressive episodes. In light of that finding they theorized that this proposed change in reactivity to stressors across the course of repeated episodes may itself be modified by genetic factors [120].

It is also important to note studies by Kaufman, Taylor and their associates which have established that a supportive environment may counteract SS predisposition to depression in abused children and even be beneficial to individuals with the SS genotype [110,121].

It has been hypothesized that these discrepancies may be explained by the assumption that other regions of the SLC6A4 interact with the functions mediated by the 5-HTTLPR polymorphism. In accordance with that theory, Lazary and associates suggested that in addition to the promoter region, the middle region, marked by the A allele of rs140700, of the SLC6A4 gene exhibits a modifying effect on gene function [122].

In light of all findings mentioned, Becker and associates suggested that the S allele of the 5-HTTLPR gene confirms a vulnerability to depression only in individuals with histories of significant stress. In the absence of these experiences, the S allele appears to contribute little to the development of depression [15].

Biological Stress Reactivity

Biological stress reactivity may also turn out to be a very important mechanism underlying the association between the serotonin transporter gene and exposure to serious life events in increasing the risk for depression. That is especially the case if we consider that serotonin system is involved in both activation and feedback control of the HPA axis, therefore having a crucial role in regulation of its activity, even though HPA axis and hormone cortisol are central elements of the biological stress reactivity theory [123]. In animals serotonin was found to activate the HPA axis by stimulating CRF [124]. Furthermore, mice with knocked out serotonin transporter gene have increased HPA axis response to acute stress [125]. Barr and associates [126] found that in infant rhesus macaques serotonin transporter gene variation affects HPA axis activity. As mentioned earlier, S allele has generally been found to be associated with greater risk for depression than LL genotype. Gotlib and associates therefore theorized that a single laboratory stressor is too mild and transient to produce cortisol production in LL and SL individuals but sufficient to provoke a cortisol response in SS participants [127]. Therefore, individuals with the SS genotype may have a lower threshold for cortisol production in response to stress.

Consistent with the idea of stress reactivity, researchers have found cortisol to be elevated in 40%–60% of adults with major depression [128]. Furthermore, some studies have provided information about the association between the S allele and elevated cortisol levels. On that note, several studies established that individuals with the SS genotype were associated with increased cortisol awakening response, although that effect was mostly seen in females [129,130]. In response to physiological stress, individuals with the SS genotype have increased plasma cortisol response compared with individuals with the L allele, but curiously this was also shown for

women only [131]. All being said, hypercortisolemia can lead to hippocampal neuronal loss, which is involved in the pathogenesis of depression [132]. Therefore, Gotlib and associates hypothesized that depressed individuals, many of whom are likely to carry the S allele [34], are characterized by hypercortisolemia not only because they have been exposed to a greater number of stressful life events than nondepressed controls [133] but also because they are biologically more reactive to stressors [134].

The idea of stress reactivity may explain both Caspi's [34] finding of an increased likelihood of developing depression in response to stressful events among S carriers and Kendler's [105] finding of the importance of low-threat events in predicting the onset of depression [127].

Personality Trait Neuroticism

As already stated, the association between the lower expressing S allele of 5-HTTLPR and susceptibility to depression in response to stressful life events is rather controversial. This inconsistency might be caused by not taking into account cognitive stress-vulnerability as a pivotal factor in predicting depression symptoms. Therefore, the interaction between 5-HTTLPR genotype and neuroticism, personality trait related to anxiety, stress reactivity and depression, might be a more powerful additional predictor of depression symptoms than gene and stressful life events interaction [135].

In a study published in 1996, Lesch and associates reported that individuals carrying the S allele displayed higher levels of neuroticism[8]. Contrary to that finding, more recent studies suggest no impact of serotonin transporter polymorphisms on neuroticism [136]. Only modest associations have been reported between the S allele and relatively increased trait negative affect [40,41,137,138]. Individuals with the S allele were also found to experience negative emotions more unpleasant, more influential, and disruptive on personal goals, as well as feel less able to cope with these emotions [139]. That could, at least partially, be explained by the hypothesis that S allele carriers experience negative events differently than non-carriers, or recall those events differently. Finding of less subjective coping ability in S allele carriers is consistent with the results of Wilhelm and associates who found that the S allele of the serotonin transporter gene is associated with the use of fewer problem-solving strategies and less efficient coping with stressful situations [140].

The S allele has been associated with relatively increased risk for depression in the context of environmental adversity [51], a relationship that may be mediated by increased neuroticism, therefore amplifying the individual's vulnerability to the experience of SLE [141]. Indeed, the presence of the S allele of the 5-HTTLPR and the experience of SLE is associated with a higher level of neuroticism [51]. Also, Jacobs and associates established that the effect of SLE on depression was no longer dependent on 5-HTTLPR after taking neuroticism into account [142].

Neuroticism itself has also been associated with depression [143] and the risk of exposure to SLE [144,145]. Positive associations between the S allele and increased trait negative affect or risk for depression have not been consistently demonstrated across studies [74,75,146]. However, data from the field of imaging genetics has provided relatively consistent evidence for a link between the S allele and relatively heightened amygdala activation to emotional stimuli relative to neu-

tral stimuli, a key neural process underlying the generation of behavioral and physiologic arousal to environmental threat [127,141].

Newer analyses confirmed that the SS allele genotype, stress experience and neuroticism are independently associated with higher depression scores. In light of that finding, Verschoor and associates established that SS genotypes exhibit vulnerability to depressive symptoms only when reporting high stress and high neuroticism scores. That indicates that not stress events per se, but rather a cognitive stress-vulnerability like neuroticism, interacts more powerfully with 5-HTTLPR genotype in promoting depression symptoms [135].

Conclusion

Everything said leads us to conclude that molecular and neural mechanisms that underlie the interplay of genes, environmental adversity and personality traits that constitute disease risk remain incompletely understood. Inconsistent conclusions observed in scientific research have proven to be the only constant finding while analyzing the possible association of serotonin transporter polymorphism and depression. Why that is the case is still to be determined but those inconsistencies may be in some cases due to genotype interaction with a variety of other factors: gender, social background, ethnic differences, as well as already discussed gene-environment interactions and serious life events, biological stress reactivity and personality traits. Furthermore, many studies addressing this issue acknowledge limitations, which often include small sample sizes, recognized or suspected variability in the clinical phenotype, and coexisting disorders. Also, it is difficult to compare across studies due to heterogeneity of the included samples.

As SLC6A4 genotyping is a relatively new field of research there are still areas that have not been examined in detail, one of those is the aforementioned tri-allelic 5-HTTLPR polymorphism. Future may indeed lead to more extensive genotyping of SLC6A4, while taking into account all newly discovered variants within the gene and its regions. Factors like life stress and environmental factors that may contribute to increased vulnerability in susceptible individuals should also be more extensively addressed as they may prove be the key to timely treatment and effective preventive strategies.

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Conflict of interest

None declared

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Povezanost polimorfizama serotoninskog transportera s depresijom

Sežatak – Serotonin se smatra jednim od najvažnijih čimbenika u modernoj psihijatriji te je značajna količina istraživanja posvećena upravo tom neurotransmiteru. Serotoninski transporter i njegovi razni polimorfizmi se smatraju povezanima s raznim psihijatrijskim poremećajima, većinom depresijom i suicidom. U svjetlu te činjenice, ovaj pregledni članak će pokušati prikazati nove podatke vezane uz polimorfizme serotoninskog transportera i njihovoj povezanosti s depresijom. Pošto je primjetan stalni porast istraživanja vezan za ovo područje psihijatrije, a koje danas uključuje i razne druge čimbenike nego što je prethodno bio slučaj, bilo je potrebno pružiti kratak pregled tih čimbenika. Stoga se u ovom članku raspravlja o polimorfizmima serotoninskog transportera i njihovoj povezanosti s gensko-okolišnim čimbenicima, modelu biološke stres reaktivnosti te crtama osobnosti, a zatim i o njihovim zajedničkim djelovanjima na depresiju. Nevezano za veličinu sveukupnog znanja i istraživanja o serotoninu, jedino konstantno saznanje pri analizi moguće veze polimorfizama serotoninskog transportera i depresije su oprečni zaključci. Stoga se može zaključiti da molekularni i neuralni mehanizmi koji se nalaze u podlozi međuodnosa gena, čimbenika okoline i crta osobnosti, a koji predstavljaju rizik za razvoj bolesti, ostaju nedovoljno dobro razjašnjeni. Zbog tih oprečnih zaključka potrebno je i dalje istraživati SLC6A4, kao i druge gene te provesti istraživanja na većem broju ispitanika. Čimbenici poput stresa i čimbenika okoline, koji mogu pridonijeti povećanoj ranjivosti osjetljivih osoba, se također moraju detaljnije istražiti, pošto bi mogli biti ključem pravovremenog liječenja i učinkovitih preventivnih strategija.

Ključne riječi: serotoninski transporter, polimorfizam serotoninskog transportera, depresija